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CHANGES IN BLOOD- AND TISSUE PROTEINS IN ANAPHYLACTIC SHOCK

By

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Much experimental and clinical work has been done on changes in the distribution and chemical composition of the blood in anaphylactic shock and the shock of traumatic haemorrhage and burns (1, 2, 8-11). The term "haemo-concentration" has been used in describing certain changes in the blood occurring in these states. The pathogenesis of these conditions has been discussed and studied in detail (1, 2, 14, 16-19). In the past it was believed that the primary tissue lesion caused the liberation of toxins which resulted in general capillary damage followed by increased permeability and loss of plasma, with changed distribution of blood in the larger capillary regions, notably the splanchnic region. It has also been claimed that a compensatory emptying of the known blood depots occurs (10).

Most recent observers have taken the fall in blood-pressure to be an indication of the degree of shock. Since many ordinary simple procedures, such as anaesthesia, surgical procedures, and the reaction of the animal to these, influence the course of the shock reaction, attempts have been made to eliminate these factors as far as possible in experimental work. From a practical point of view the most easily reproduced type of experimental shock is so-called "haemorrhagic shock". In these experiments the assessment of the plasma concentration and the state of the plasma proteins is difficult. In other investigations experimental burns and traumatic shock have been used, many authors claiming to have demonstrated that the leakage of plasma to the affected area,

"a third fluid space" (Randall, 13), is sufficient to explain the haemo-concentration. Wiggers (19) summarizes: "The general conclusions appear to be that loss of plasma protein is common to all forms of oligemic shock".

Concerning the metabolic changes during shock Engel (1) states: All of the metabolic changes described during shock can be attributed to the consequences of hypoxia affecting different organs and tissues of the body to varying degrees and that death seemingly results from disorganization at the cellular and enzymatic level. In short, the metabolic changes are the result and not the cause of the circulatory failure".

The course of experimental *anaphylactic* shock varies from one species of animals to another. It has been shown that specific shock organs exist for every species.

Organs which contain well-developed smooth muscle react strongly in anaphylactic shock. In the guinea-pig, which has been the most commonly used animal in these experiments, acute and protracted shock can be distinguished.

Acute shock is commonly precipitated by intravenous injection or inhalation of antigen, and is followed, after a few minutes' severe air-hunger, by death from asphyxia. It resembles histamine or peptone shock. In *protracted shock*, which is brought about by intraperitoneal or subcutaneous administration of antigen, the animal develops, after a latent period of about 10 minutes, gradually increasing respiratory distress together with marked general depression; the final stage is, as in acute shock, severe air-hunger and asphyxia, and signs of cerebral involvement suggesting cerebral anoxia are commonly seen. The course of the shock varies from 30 minutes to several hours, depending on the dose of antigen and the degree of sensitization.

In *protracted shock* certain typical changes resembling haemoconcentration occur in the composition of the blood, and these have been studied in some detail in the present work. At the same time quantitative changes can be demonstrated in the protein concentration of the plasma and the shock organ.

Most cases of allergy in man consist of a slight, protracted reaction such as urticaria, allergic rhinitis, and asthma. A proportion of cases correspond to a more severe, protracted state of shock (status asthmaticus). A few cases correspond-

ing to acute shock also occur (serum shock, acute drug reactions). The changes in blood and plasma to be expected most commonly in human pathology would thus appear to correspond most closely to the changes in protracted shock in animals.

The long-discussed question of the mechanism of allergic shock is very close to the arguments of recent years on the pathogenesis of traumatic shock, *vide* the attempts to demonstrate anaphylatoxin, H-substances, histamine, acetylcholine, etc. It may be that these two problems in fact overlap. Thus the difficulty of demonstrating the toxic agent in the blood of shocked animals has been common to both. It has been remarked that the supposed toxin never occurs in the blood in amounts great enough to cause shock if injected into a healthy animal. Experience has also shown that considerable amounts of peptone must be given intravenously to precipitate this type of shock.

The loss of plasma in burn shock and traumatic shock has been the subject of recent study (see above). If the latest theories on traumatic shock apply also to allergic shock the shock organ forms a third space. If this is so the haemoconcentration and other blood changes occurring in allergic shock can be explained by loss of plasma to the organ concerned.

It is improbable that any significant haemoconcentration takes place in ordinary allergic states in man. It is however possible that this factor comes into play in severer reactions, and may exercise an important influence on the course of the disease process. It must however be kept in mind that compensatory counter-reactions with certainty quickly arise and develop, so that the picture becomes complicated. As long ago as 1914 Widal and associates (18) demonstrated changes in the blood and plasma in certain human allergic states. These "haemotoclastic crises" consisted of haemoconcentration, lowering of the refractive index of the serum, and increase in the dialysable substances of the serum, and took place during acute stage of the allergic reaction. This interesting observation has re-appeared in recent literature, but so far as I have

been able to make out has not been the object of detailed study. It would therefore be of interest to attempt to measure the blood and plasma protein changes in severe protracted fatal shock in animals.

A large number of experimental animals has been at my disposal in connexion with the studies on proteolysis in the shock organ, and the material available has been re-treated with regard to the subject in question.

MATERIAL AND METHODS

Male guinea-pigs weighing 300–450 g (yellow Danish type) from the same strain were used. They were kept in large open cages, and were fed on a diet of hay, swedes, and oat-bran. *Sensitization*: one ml. of 3 % solution of dried egg-albumen intraperitoneally.

Specimen-taking and precipitation of shock. The left jugular vein is exposed under light ether anaesthesia, 1.5 ml. of blood withdrawn, and the blood-sample oxalated. The animal, which immediately regains consciousness, is at once given intraperitoneally 1.2 ml. of 3 % egg-albumen per 100 g. body-weight. Signs of shock begin to appear in the sensitized animal after about 10 minutes, and typical anaphylactic shock, ending in death, within 20–40 minutes. In about 20 % of the animals fatal shock did not occur within one hour, and these animals have been excluded from the series; some of them were examined after anaesthesia (see below). Immediately after death the thorax was opened and the apex of the beating heart snipped off. Blood was collected in an oxalated tube, and the lungs were removed for further preparation. The non-sensitized controls, every other animal, were killed at a corresponding point after intraperitoneal injection of antigen by means of ether anaesthesia, and were treated in the same way.

Lung extract. The thoroughly rinsed lungs, briefly dried off on filter-paper, were ground with sterile sand, and mixed

with three times their weight of physiological saline: dilution thus 1:4. The sediment was centrifuged off for 1 minute at 1000 revolutions per minute¹.

CHEMICAL PROCEDURES

1. Estimation of total N by Kjeldahl's method (micro-modification).
2. Estimation of amino-N by von Slyke's method.
3. Estimation of fibrinogen. The plasma diluted 10x: recalcification + addition of thrombin; coagulation at 37° C. for 30 minutes; the coagulate centrifuged and washed repeatedly with distilled water; total N then determined.

The estimation of total N was done, on plasma and lung extract, and on the supernatant after coagulation on a water-bath at 60° C. for 1 hour followed by centrifuging. The amino-N determinations were done before and after 2 hours digestion of the lung extract under optimal conditions (cf. Herberts 5).

OTHER PROCEDURES

The blood volume was measured in a graduated tube. Haematocrit readings (double determinations) were done in most cases both before and after shock. Red cell counts were done on the same samples in 10 cases.

Necropsy was performed on all the animals, and only those apparently healthy on macroscopic examination have been included in the series. (In a few isolated cases resolving cervical adenitis was found). To a limited extent histological sections were done to check the lung findings.

No signs of increased engorgement of the thoracic or abdominal viscera were found at necropsy.

¹ The protein concentration of the lung tissue was calculated from the T.N. in the extract (Kjeldahl). This value exceeded 95 per cent of the T.N. of fresh lung tissue (Keldahl).

RESULTS

Bleeding volume. This was constantly diminished in the shock series, but since losses during the procedure of exsanguination could not always be avoided the figures have not been treated statistically. In the controls the amount of blood obtained was 6–10 ml., and in the shock series 1–3 ml. As can be judged from the figures (which differ widely), the difference must clearly be established.

Haematocrit readings. (16–20 animals in each series).

1. Untreated	Mean = 34.3 ± 0.98
2. The same animals 20–40 min. after administration of antigen intraperitoneally	Mean = 31.5 ± 1.09
3. Shocked animals 20–40 min. after administration of antigen intraperitoneally	Mean = 37.0 ± 0.91
Differences	
1–2 =	2.8 ± 1.47
1–3 =	-2.7 ± 1.33
2–3 =	-5.5 ± 1.42 (significant)

From the difference between group 2 and group 3 is apparent that the shock has caused an increase in the haematocrit readings.

RED CELL COUNT

The taking of blood samples and the intraperitoneal administration of antigen fluid in *healthy* animals resulted in a fall in the red cell count by 11.8 % (at a point corresponding to the time of death in the sensitized series).

After *protracted shock* (the sensitized series), on the other hand, an increase of 19.2 % compared with the initial value was found. *Acute shock* raised the value by 10.4 %. The figures are the means of 10 double estimations in each series.

Tables 1 and 2 give the concentration of plasma proteins and fibrinogen in healthy and shocked animals respectively. Column 1 shows the initial values; column 2 shows the values after fatal shock, or in the healthy series after killing at a

TABLE 1

*N-concentration in plasma (Kjeldahl)—mg. per 100 ml.
Healthy animals.*

No.	Plasma		Fibrinogen		Fibrinogen/plasma %	
	1	2	1	2	1	2
64	659	578	66	—	10.0	—
65	640	600	—	—	—	—
76	700	577	44	—	5.9	—
86	790	660	79	75	10.0	11.4
87	761	668	78	68	10.3	10.2
88	734	605	89	85	12.1	14.1
89	788	720	78	76	9.9	10.5
91	706	654	55	49	7.8	7.5
99	710	659	60	56	8.4	8.5
101	750	693	—	—	—	—
103	790	645	67	63	8.5	9.8
105	787	612	73	47	6.0	7.7
107	768	544	51	31	4.0	5.7
108	846	625	53	50	5.9	8.0
109	—	653	—	84	—	12.8
110	661	631	—	70	—	11.1
111	655	643	53	34	8.1	5.3
112	612	575	—	44	—	7.7
114	776	598	—	—	—	—
130	818	756	—	74	—	5.7
131	803	684	71	80	8.8	11.7
132	836	798	—	—	—	—
140	838	762	82	80	9.8	10.5
M	747	650	66	61	8.4	9.3
	± 13.7	± 12.5	± 3.3	± 4.5	± 0.6	± 0.6

1 = initial N-concentration.

2 = N-concentration 20-40 min. after intraperitoneal injection of antigen.

corresponding point of time. This column in the healthy series is intended to give an idea of the effect on a healthy animal of similar procedures (anaesthesia, sample-taking, intraperitoneal administration of fluid).

Table 3 shows the differences. Column 2 gives the true difference with regard to the significance of the shock. Table

TABLE 2
*N-concentration in plasma (Kjeldahl)—mg. per 100 ml.
 Shocked animals.*

No.	Plasma		Fibrinogen		Fibrinogen/plasma %	
	1	2	1	2	1	2
68	832	536	—	—	—	—
71	836	425	55	54	6.5	12.7
78	730	579	—	—	—	—
81	846	469	50	29	5.9	6.2
82	788	451	81	41	10.3	9.1
83	776	431	68	30	8.6	7.0
85	688	461	58	46	8.4	9.9
92	798	492	62	—	7.7	—
93	822	356	64	—	7.8	—
95	749	498	70	64	9.4	12.8
96	782	420	69	47	8.9	11.2
97	744	428	44	24	5.9	5.6
98	690	425	60	43	8.7	10.2
102	765	483	92	40	12.0	8.2
100	771	395	55	39	7.1	9.9
113	813	495	—	—	—	—
115	730	450	—	33	—	7.3
116	773	450	—	—	—	—
117	739	512	—	—	—	—
118	782	569	—	39	—	6.9
119	803	586	62	41	7.7	6.9
120	777	559	74	37	9.5	6.6
121	830	575	45	34	5.4	5.9
122	753	580	—	—	—	—
124	688	466	95	72	13.8	15.5
125	714	536	62	46	8.7	8.6
126	837	692	—	—	—	—
127	669	565	81	—	12.1	—
M	774	496	66	42	8.7	8.9
	± 10.1	± 13.5	± 3.1	± 2.8	± 0.5	± 0.7

1 = initial N-concentration.

2 = N-concentration 20-40 min. after intraperitoneal injection of antigen.

TABLE 3

Difference between the N-concentration in healthy and sensitized animals.

	Plasma		Fibrinogen	
	1	2	1	2
Healthy animals	747 $\pm$ 13.7	650 $\pm$ 12.5	66 $\pm$ 3.3	61 $\pm$ 4.5
Sensitized animals ...	774 $\pm$ 10.1	496 $\pm$ 13.5	66 $\pm$ 3.1	42 $\pm$ 2.8
Diff.	27 $\pm$ 17.0	154 $\pm$ 18.4 24 %	—	19 $\pm$ 5.3 31 %

1 = initial concentration.
2 = concentration after intraperitoneal injection of antigen.

TABLE 4

Difference in N-concentration of plasma from sensitized animals before and after shock (individual animal).

	Plasma	Fibrinogen
Before shock	774 $\pm$ 10.1	66 $\pm$ 3.1
After shock	496 $\pm$ 13.5	42 $\pm$ 2.8
Diff.	278 $\pm$ 16.9 36 %	24 $\pm$ 4.2 36 %

4 on the other hand gives the greatest difference between values from individual animals: this difference thus also embraces the effect of the procedures named above.

It will be seen from the tables that the plasma nitrogen in guinea-pigs is normally about 750–770 mg. per 100 ml., and that it falls to 650 mg. after sample taking and administration of antigen fluid. The fibrinogen accounts for a good 8 % of the plasma nitrogen.

A considerable fall in the plasma nitrogen takes place after shock (to 500 mg. per 100 ml.).

The fall due to the actual shock (Table 3) amounts to almost one fourth of the initial value. The fibrinogen too falls sharply in the shock series, with the result that the relative concentration of fibrinogen in the plasma remains constant.

The lung-weights, the nitrogen concentration in lung ex-

TABLE 5
N-concentration in lung-extract (Kjeldahl) mg. per 100 ml.
Healthy animals.

No.	Lung weight in g	Extract ¹	Remainder after heat- coagulation at 60° C ²
64	3.8	330	—
65	4.2	322	170
76	3.7	324	191
86	3.8	315	197
87	—	292	256
88	—	265	226
89	—	264	238
91	—	288	187
99	—	276	191
101	—	314	199
103	—	242	—
105	5.1	328	206
107	5.8	378	—
109	5.5	285	214
110	4.0	292	—
111	5.3	345	232
112	5.0	287	214
114	5.8	324	228
130	5.0	350	175
131	3.2	341	201
132	3.2	230	248
140	3.0	261	152
141	—	236	211
142	—	320	142
144	—	356	178
145	—	338	162
146	2.9	330	234
M	4.3 ± 0.25	305 ± 6.6	203 ± 6.1

¹ Dilution of the extract 1:4.

² Supernatant fluid after coagulation at 60°C for 30 min.

tract, and the nitrogen concentration in the supernatant after coagulation at 60° C., are given in Tables 5 and 6. The difference between healthy and shocked animals can be seen in Table 7: an increase in lung-weight takes place in the shock

TABLE 6
N-concentration in lung-extract (Kjeldahl) mg. per 100 ml.
Shocked animals.

No.	Lung weight in g	Extract ¹	Remainder after heat- coagulation at 60° C. ²
68	—	345	—
71	—	337	178
81	—	425	237
82	—	402	203
83	—	430	214
85	4.8	451	206
92	4.0	410	275
93	5.5	376	246
95	6.1	308	288
96	6.0	283	261
97	5.7	340	195
98	4.6	308	191
100	4.7	370	175
102	4.5	356	195
113	5.7	324	216
115	5.3	310	—
116	5.5	288	197
117	4.6	372	201
118	5.3	294	218
119	5.4	275	201
120	5.5	288	236
121	5.5	332	285
122	5.2	287	267
124	5.2	282	242
125	5.2	392	—
126	5.4	347	220
127	5.7	275	222
128	7.4	334	212
129	—	462	209
134	—	290	293
135	—	460	316
136	3.5	331	236
137	6.5	349	234
143	6.5	374	222
M	5.4 ± 0.16	347 ± 9.5	232 ± 6.8

¹ Dilution of the extract 1:4.

² Supernatant fluid after coagulation at 60°C for 30 min.

TABLE 7

Difference between N-concentration of lung extract in healthy and shocked animals.

	Lung weight in g	Extract	Remainder after heat-coagulation at 60° C.
Healthy animals	4.3 ± 0.25	305 ± 6.6	202 ± 6.4
Shocked animals	5.4 ± 0.16	347 ± 9.5	232 ± 6.8
Diff.	1.2 ± 0.30 28 %	42 ± 11.5 13 %	30 ± 9.2 15 %

series simultaneously with an increase in nitrogen. The percentage concentration of heat-coagulable fraction in lung extract however remains constant.

In assessing this table it should be borne in mind that the lung extract was diluted in relation to the lung-weight. The total increase in nitrogen in the whole lung amounted to 22.5 mg. N¹.

*Fe-determinations*². Lung extracts (dilution 1:10) prepared from 9 healthy animals (controls) contained 2.7–4.4γ Fe per ml. (mean = 3.5γ). The corresponding figure for 10 shock lung extracts was 4.1–9.5γ Fe per ml. (mean = 6.5γ per ml.). 1 ml. blood contains 535γ Fe. These figures correspond to a blood volume in healthy lung (40 ml. extract) of 0.26 ml. of blood (140 γ), and in shock lung (50 ml. extract) of 0.61 ml. of blood (325 γ). The post-shock increase in lung blood thus amounted to 0.35 ml.

It has been shown in previous experiments that proteolytic digestion occurs in lung extract, and this phenomenon has also been evident in the present series (material partly common to both investigations).

¹ Calculation as follows.

T.N. in normal lung = $3.05 \times 4 \times 4.3 = 52.5$ mg

T.N. in shock lung = $3.47 \times 4 \times 5.4 = 75.0$ mg

Difference = 22.5 mg N

² Carried out at the Institute of Med. Chemistry by M.D. Bo Hallgren.

DISCUSSION

The reduced bleeding volume and the raised red cell count and haematocrit reading indicate that haemoconcentration developed after shock. The haemoconcentration measured in this manner was affected in the opposite direction by the various procedures carried out on the animals (taking of initial blood sample, intraperitoneal injection of fluid). The phenomenon of counter-shock too probably affects the findings during the course of protracted shock.

The fall in the plasma-protein concentration during shock amounts to about 25 %. Thus *in association with the haemoconcentration mentioned above considerable dilution of the plasma occurs*. This can be explained by passage of protein from the plasma to the tissues. The fall in the plasma proteins is also influenced by the initial procedures, though to only an inconsiderable degree¹. This is also apparent from the fact that a similar, though lesser, fall can be seen after acute shock (0.3 ml. antigen fluid iv.), and a much greater fall seen after protracted histamine shock² even in cases where neither initial blood samples are taken nor fluid is administered intraperitoneally.

The fibrinogen concentration remains constant in relation to the plasma protein level. The well-known fact that coagulation is delayed after anaphylactic shock in the dog is attributed to heparin release, and this is explained by the severe liver shock occurring in this animal. The corresponding conditions in the guinea-pig were investigated as follows.

If a suitable quantity of heparin antagonist (toluene blue or protamine sulphate) is added to bloods from healthy and shocked animals an increase in the measurable fibrinogen concentration is obtained which is greater in the shock blood. This would suggest that liberation of heparin also occurs in the guinea-pig in allergic shock. However Rocha E Silva (15) has shown that protamine strongly affects the proteolytic processes after shock. It is possible that in

¹ Compare the values in non-sensitized animals (table 3).

² Experiments with histamine shock have been performed in connexion with another study to be published later.

shock proteolysis may also engage some of the components in the coagulation system [cf. Nolf (12), Rocha E Silva (15)]. Addition of protamine would then affect both proteolysis and coagulation. Some fibrinolysis experiments indicate such a course.

The increase in protein concentration of the lung (about 40 %) accounts for part of the loss of protein from the plasma. Even though in guinea-pigs the actual shock organ is the lung, it is probable that other highly vascular organs containing much smooth muscle take part in the allergic reaction. Clinical signs from such organs are often seen in the early course of shock, signs such as severe rhinorrhoea, incontinence of urine and faeces, etc. Leakage of plasma from the blood-stream to these organs is not improbable.

The protein concentration in post-shock lung extract will be influenced both by the altered blood distribution, "sequestration", (dilated capillaries, changed blood-content) and by leakage of plasma into the lung tissue. As previously mentioned, the increase in bleeding volume in the shock lung amounts to 0.35 ml. This accounts for about 9 mg. of the total nitrogen increase of 22.5 mg., in the lung. The remainder can only be explained by the leakage of protein from plasma into the tissue. Since the increase in lung-weight in the shock series averages 1 g., other factors must be involved, as deposition of plasma (0.65 ml.) would account for only 5 mg. of nitrogen; the increase in lung-protein must be conditioned by a selective passage of fluid with high N-content or by stagnation of protein in the shock organ with resorption of water.

CONCLUSION

Guinea-pigs exposed to serious fatal protracted shock show:

1. signs of haemoconcentration, calculated from an increase in corpuscular elements in the blood and increased haematocrit readings,
2. considerably diminished volume of circulating blood,

3. decreased plasma protein values (about 25 %), and
4. increased lung weight (shock-organ) and high protein concentration in lung tissue (40 % increase).

The results from points 2 and 3 above show that a considerable loss of protein from the plasma has taken place. In many cases of protracted shock, already in 20 min., the remaining part of protein in the plasma is less than half the initial value. A certain part of the protein loss can be the result of stagnation of blood in dilated capillaries. This part is however of little magnitude (cf. the Fe-content in the shock organ above). The larger part of the protein loss is probably to be found in the interstitial fluid or in the cells (cf. the protein increase of the lymph after peptone shock). Such an increased protein content in the extra-cellular fluid may cause an altered cell function.

The metabolic alterations during anaphylactic shock described in earlier papers (4, 5) and the changes in blood and tissue protein, shown above, cannot be explained by Engel's conclusion concerning the corresponding changes in traumatic shock. Some new aspects on this problem will be given in a subsequent paper.

SUMMARY

Guinea-pigs exposed to serious fatal protracted shock show haemoconcentration, considerably diminished bleeding volume, decreased plasma protein values and high protein concentration in lung tissue. The findings indicate an increased protein content of the extra cellular fluid, resulting in disturbed cell function.

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